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Atypical Presentations of Atypical Antipsychotics

ABSTRACT

The atypical antipsychotics have been touted by many as having minimal extrapyramidal symptoms. This case series from the Tripler Army Medical Center Psychiatry Graduate Medical Education Program presents the extrapyramidal symptoms observed with four different atypical antipsychotic medications. Also reviewed are the mechanisms of action that atypical antipsychotics and first-generation antipsychotics use to treat the symptoms of schizophrenia. Cases reviewed include a schizophrenic male patient whose dose of risperidone was doubled from 6mg to 12mg overnight and developed an acute dystonic reaction; a young male patient with a substance-induced psychosis who unintentionally doubled his ziprasidone dose in 24 hours, resulting in an acute dystonic reaction; a young female patient on paroxetine who also recently started olanzapine and had complaints consistent with akathisia that resolved with treatment; and an adolescent female patient on escitalopram for obsessive-compulsive disorder who after starting aripiprazole developed Parkinsonism. All four cases illustrate that even though atypical antipsychotics are less likely to cause extrapyramidal symptoms than their first generation cousins, the physician should be aware that these symptoms may still occur and need to be treated.



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INTRODUCTION

Schizophrenia continues to affect one percent of the population, with the age of onset usually prior to 25 years old, continuing throughout life, and crossing all social classes. The introduction of antipsychotic medication has greatly enhanced the quality of life for patients with schizophrenia, and ongoing research is being conducted to further the understanding of the disease.¹

Prominent expert in psychopharmacology, Stephen M. Stahl, MD, PhD, discussed that the focus of the biologic treatment for this disease centers around the monoamine neurotransmitter dopamine and its four key pathways. An excess of dopamine in the mesolimbic pathway with projections from the midbrain ventral tegmental area to the nucleus

to a primary deficiency of dopamine or a secondary deficiency caused by excess serotonin inhibiting dopamine release.

Dopamine neurons project from the hypothalamus to the anterior pituitary within the tuberoinfundibular pathway and inhibition of dopamine increases the hormone prolactin, leading to galactorrhea; amenorrhea; breast engorgement in females; gynecomastia in men; and possible sexual dysfunction (Figure 1).²

The nigrostriatal pathway is part of the extrapyramidal nervous system projecting from the substantia nigra in the brainstem to the basal ganglia and the striatum and is critical in the regulation of motor movement.² Excess of dopamine in this pathway is associated with hyperkinetic movement disorders, such as

ing out of their skin. Onset is usually days to weeks after initiation of treatment and can often be incorrectly diagnosed as anxiety or worsening psychosis instead of EPS. Dystonia, an acute spasm of muscle groups, often presents with a fixed upper gaze, twisted neck or torticollis, and facial muscle spasms resulting in grimacing, clenched jaw, and difficulty in speech. The condition is often painful and can be frightening, usually occurring soon after antipsychotic treatment is initiated. Parkinsonism is characterized by rigidity, bradykinesia, shuffling gait, resting tremor or pill-rolling finger movements, slow monotonous speech, and/or masked facies. While EPS is usually short-lived and reversible, it is thought that long-term blockade and upregulation of D2 receptors in

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accumbens is associated with the positive symptoms of schizophrenia, such as hallucinations and delusions, and will produce more or less of these symptoms in proportion to changes in dopamine levels.² The mesocortical pathway is associated with the negative and possibly some of the cognitive deficits seen in schizophrenia due to a deficiency in dopamine from the midbrain ventral tegmental area projecting to the limbic cortex.² Such symptoms may be due

chorea, tics, and dyskinesias. Deficiency of dopamine in this pathway is associated with extrapyramidal symptoms or side effects (EPS), the three most common being akathisia, acute dystonia, and Parkinsonism. Akathisia is a form of agitation and internal restlessness characterized by the patient's inability to sit still, pacing, rocking and shifting of weight while standing, and tapping of feet. Patients will often describe that they feel like crawl-

ing out of their skin. Onset is usually days to weeks after initiation of treatment and can often be incorrectly diagnosed as anxiety or worsening psychosis instead of EPS. Dystonia, an acute spasm of muscle groups, often presents with a fixed upper gaze, twisted neck or torticollis, and facial muscle spasms resulting in grimacing, clenched jaw, and difficulty in speech. The condition is often painful and can be frightening, usually occurring soon after antipsychotic treatment is initiated. Parkinsonism is characterized by rigidity, bradykinesia, shuffling gait, resting tremor or pill-rolling finger movements, slow monotonous speech, and/or masked facies. While EPS is usually short-lived and reversible, it is thought that long-term blockade and upregulation of D2 receptors in



FIGURE 1. Increased serotonergic activity in the Substantia Nigra and Basal Ganglia-Neostriatum leads to decreased release of dopamine in the Nigrostriatal Pathway.

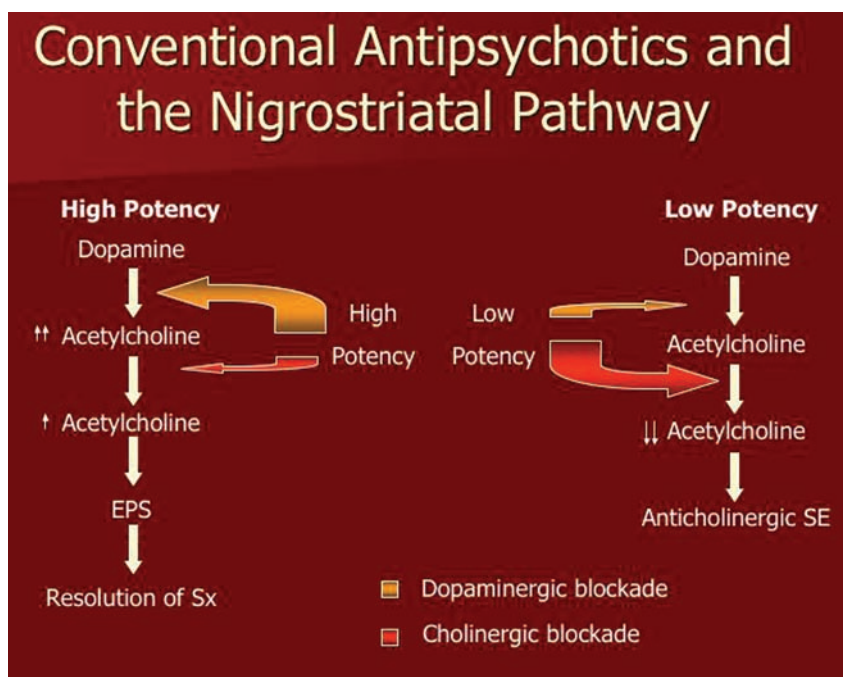


FIGURE 2. Conventional antipsychotics can be divided by low and high potency. High potency antipsychotics have a higher dopaminergic blockade in the nigrostriatal pathway leading to increased potential for EPS. Low potency antipsychotics have a higher cholinergic blockade leading to increased potential for anticholinergic side-effects.

clonic movements of the spine. Although all the traditional antipsychotics cause tardive dyskinesia, some evidence suggests that the newer atypical antipsychotics may be less likely to do so.

Nomenclature within the two recognized antipsychotic medication classes varies. The first antipsychotics discovered strongly inhibit dopamine receptors and are aptly called dopamine recep-

tor antagonists but are also referred to as first-generation, traditional, or conventional antipsychotics (Figure 2). This class of antipsychotic medication was introduced in the 1950s after chlorpromazine, initially used for its antihistaminic properties, was noted to lessen psychotic symptoms in schizophrenic patients.⁷ All medications within this class block the D2 dopamine receptor and individual side effect profiles are based upon potency, and indicative of how much a drug will bind to the D2 receptor.³ A reciprocal relationship between dopamine and acetylcholine exists within the nigrostriatal pathway directly impacting the severity of EPS. Dopamine will suppress the release of acetylcholine from postsynaptic cholinergic neurons. However, if dopamine receptors are blocked by a first generation antipsychotic medication, then limited dopamine will be available to check the release of acetylcholine postsynaptically resulting in EPS. The concomitant use of an anticholinergic agent will decrease the symptoms by directly blocking acetylcholine receptors. Lower potency conventional antipsychotics (Figure 2) with prominent cholinergic receptor blockade, such as chlorpromazine, will have a lower incidence of EPS than high potency medications from this class with limited cholinergic receptor blockade such as haloperidol. All medications within this class have the same mechanism of action by blockade of the D2 receptor with potency determined by receptor affinity, and side effect profiles determined by the degree of blockade at muscarinic-cholinergic, α 1 adrenergic, and histaminic receptors.

By the 1990s, a new class of antipsychotics known as the serotonin-dopamine antagonists, second generation antipsychotics or atypical antipsychotics (Figure 3), were approved for use by the

Food and Drug Administration (FDA). This class was considered an improvement by allegedly providing better negative symptom efficacy, less impaired cognition, and lower risk of extrapyramidal symptoms.⁴ (For consistency, the terms *conventional* and *atypical* antipsychotics will be used throughout this paper).

Despite being initially marketed as having a less significant side-effect profile compared to the conventional antipsychotics, atypical antipsychotics are not without potential complications. Evidence suggests that several drugs in this class may be associated with significant weight gain, lipid abnormalities, and risk of developing diabetes mellitus.³ Atypical antipsychotics have a mechanism of action involving both 5-HT_{2A} and D₂ receptor antagonism, thereby improving positive symptoms (the mesolimbic system), and causing fewer extra-pyramidal symptoms (the nigrostriatal system) than first generation antipsychotics.³ 5-HT_{2A} antagonism is key to the effectiveness of the atypical antipsychotics affecting the four dopaminergic pathways by inhibiting dopamine release from the axon terminals to varying degree according to its pathway. In the nigrostriatal pathway, serotonin released from a serotonergic axon in the raphe nucleus binds to a 5HT_{2A} heteroreceptor on a dopaminergic neuron in the substantia nigra inhibiting the release of dopamine at the axon terminal in the basal ganglia-neostriatum. Inhibition of dopamine release also occurs when serotonin binds to 5HT_{2A} heteroreceptors at the axon terminal. Because blockade of D₂ dopamine receptors in the nigrostriatal pathway may result in EPS, the goal of atypical antipsychotics within this pathway is to enhance the release of dopamine by blocking 5HT_{2A} heteroreceptors. Simultaneously, dopamine D₂ antagonism is occurring and the extra dopamine in

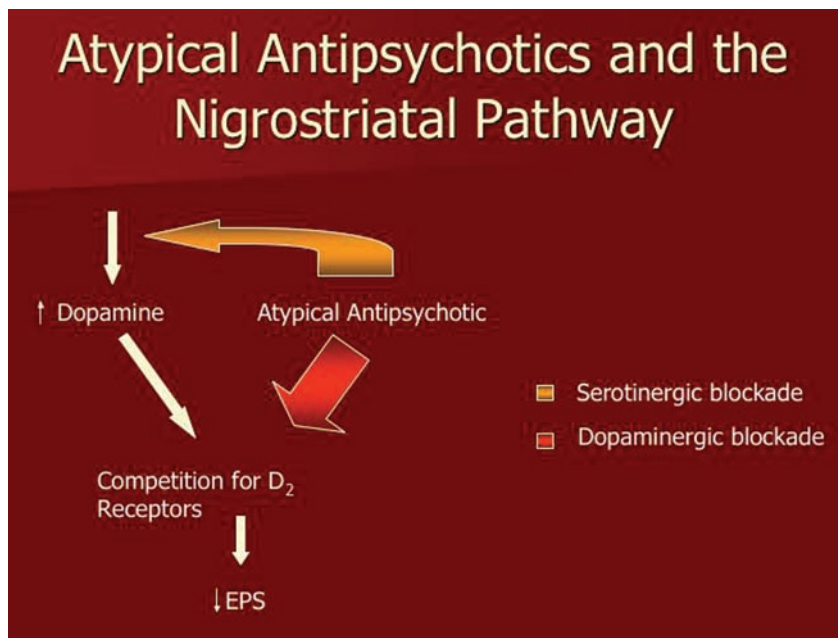


FIGURE 3. In the Nigrostriatal Pathway, serotonergic blockade causes an increase in dopamine release. Simultaneously, dopaminergic blockade causes competition for D₂ receptors leading to decreased probability of EPS.

the synaptic cleft competes with this D₂ blockade post-synaptically, resulting in more dopamine binding and less receptor blockade. Such competition at the receptor site for D₂ antagonism and dopamine stimulation is dependent on the drug, the dose, and the path to the brain.

CASE ONE

Patient A was an 18-year-old African American man with a history of mild mental retardation and schizophrenia, undifferentiated type, who was psychiatrically hospitalized due to increasingly disorganized thought processes and active auditory hallucinations. From collateral information, the patient's exacerbation of positive symptoms was thought to be due to changes in home environment (death of family member) and unknown medication adherence. The patient was on risperidone (Risperdal®, Janssen Pharmaceutica) 2mg PO BID as an outpatient and titrated to a higher dosage for better control of symptoms while in the hospital. The medication was increased to 3mg risperidone PO twice a day

on hospital Day 2. The patient had received haloperidol in the past but had no known history of EPS.

A fourth-year neurology resident and a staff psychiatrist followed this patient's case. In consultation with the treatment team, an increase in the patient's dosage of risperidone was made. In late afternoon, the patient's resident looked up the dosage of risperidone in a commonly used pharmacopoeia (Tarascon's).⁵ The maximum dosage of risperidone was listed as 16mg daily so the neurology resident decided to increase the dosage of risperidone to 6mg PO twice a day. The patient received his first evening dose of 6mg without significant side effect.

The patient received the morning dosage of risperidone 6mg at approximately 7:00 AM. Within 30 minutes, nursing staff noted that the patient had neck muscle rigidity and upward deviating eyes consistent with an acute dystonic reaction. The on-call psychiatrist arrived and deemed that the patient did have dystonia without evidence of airway compromise. The patient initially received

diphenhydramine 25mg IM; however, when he did not appear to respond within three minutes, he received another 25mg IM, and his symptoms abated in the next two minutes with further improvement over the next fifteen minutes. The patient did not note feeling drowsy, likely a side effect of diphenhydramine, but was without further complications. The risperidone, decreased to the previous dosage of 3mg BID and augmented with a second atypical antipsychotic and benztropine (Cogentin®, Merck & Co.), provided symptom relief for this patient.

CASE TWO

Patient B was a mixed race Pacific Islander in his third decade with a history of methamphetamine, opiate, and cannabis abuse. He presented to a local emergency room; admitted to the inpatient psychiatry ward for paranoid ideations, insomnia, agitation, anorexia, and hypervigilance; and stabilized on 80mg ziprasidone (Geodon®, Pfizer Inc.) PO twice daily during acute detoxification with eventual resolution of the paranoid and manic symptoms. He was also started on venlafaxine (Effexor®, Wyeth Pharmaceuticals) 150mg PO daily for his depressed mood and subsequently transferred to a local addiction rehabilitation facility. On the day of transfer, he indicated that he still needed his nighttime dose of 80mg ziprasidone and was given the requested dose. Unknown to the medical staff, he had already self-medicated with three 80mg doses, an aggregate 24-hour dose of 240mg. Within an hour after his fourth dose of ziprasidone, he developed a painful torticollis and was treated immediately with 50mg of diphenhydramine PO, resolving the acute dystonia within 20 minutes. Once this patient restarted taking his medications as prescribed, he exhibited no further dystonic reactions.

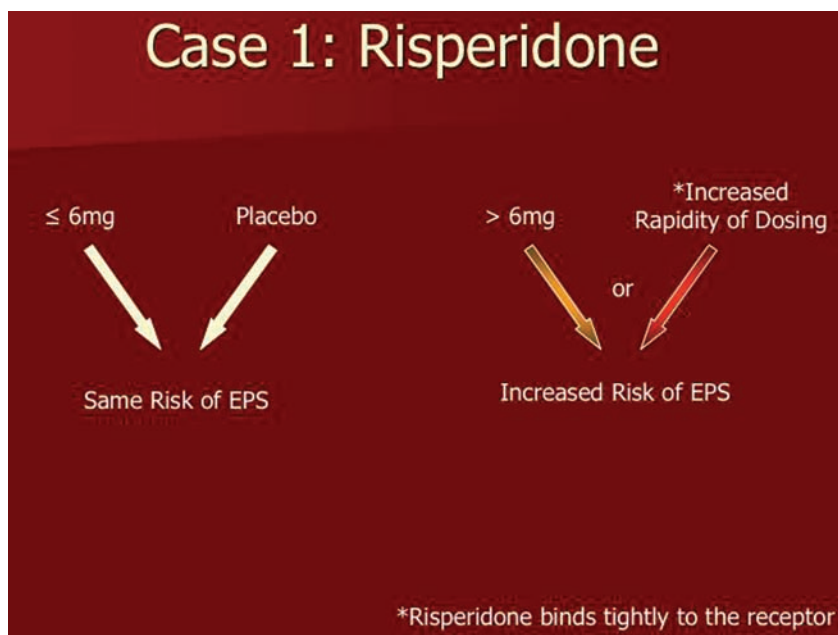


FIGURE 4. Six milligrams or less of risperidone and placebo have equivalent risk of EPS. Greater than 6mg of risperidone and/or increased rapidity of dosing leads to an increased risk of EPS.

CASE THREE

Patient C was a 26-year-old Caucasian woman with a history of major depressive disorder who presented to the outpatient psychiatry clinic acutely for complaints of a sense of restlessness and feelings like she wanted to jump out of her skin. She had been prescribed olanzapine (Zyprexa®, Eli Lilly) 2.5mg PO qhs for anxiety and insomnia six days prior, noting significant improvement in her symptoms. She was also on paroxetine (Paxil®, GlaxoSmithKline) 40mg PO qhs for her depression, denied any depressive symptoms, and felt that her depression had been well controlled. She denied suicidal ideation, but noted she would resort to the cutting behavior that was part of her baseline coping mechanism if not helped with the new restless feeling. On the Abnormal Involuntary Movement Scale (AIMS) evaluation, she scored a four on lower extremity movement, a three for severity of abnormal movements, a two for incapacitation of abnormal movements, a four for awareness, and all other scores were zero, for a score totaling 13. The patient was given diphenhy-

dramine 50mg PO and told to return to the clinic in one hour. Upon return her symptoms were significantly reduced. She complained of mild sedation, but when informed that the dose could be lowered to 25mg prn she declined, stating she was willing to tolerate the sedation in order to be rid of her akathisia.

CASE FOUR

Patient D was a 16-year-old Chinese-Japanese female patient who was admitted to a local child and adolescent inpatient psychiatry hospital for refractory obsessive-compulsive disorder resulting in academic failure and subsequent school refusal. Medications on admission included escitalopram (Lexapro®, Forest Laboratories) 60mg PO qd and quetiapine (Seroquel®, Astra Zeneca) 25mg PO at bedtime. She was nonadherent with her quetiapine and because her escitalopram had reached its maximum dosage, a new medication was added to her regimen. Aripiprazole (Abilify®, Bristol Myers Squibb) was selected for its serotonergic properties, and the patient started on 15mg PO qhs. Within one

Case 2: Ziprasidone

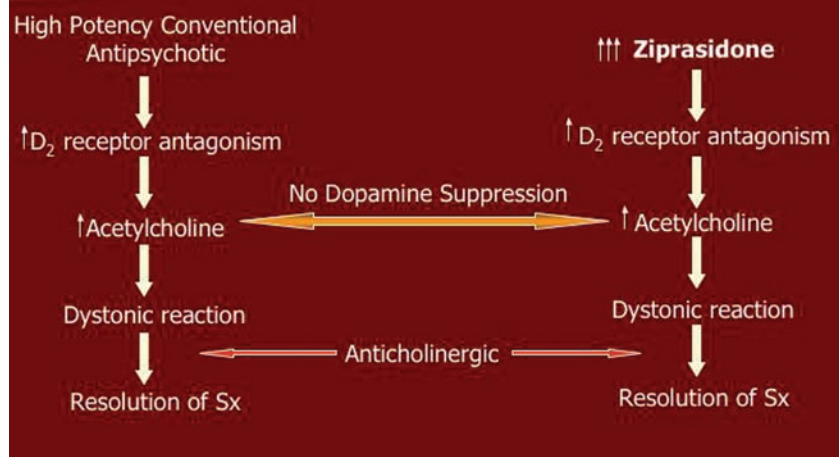


FIGURE 5. Increased levels of ziprasidone act similarly to a high potency conventional antipsychotic.

day of starting the medication, the patient complained of jaw stiffness and a change in her speech. She began to talk as though she were deliberately clamping her teeth together. She was subsequently started on diphenhydramine 25mg PO q4-6h prn stiffness. She took several doses of diphenhydramine, but experienced extreme drowsiness, and adherence was low due to sedation interfering with school performance. Within one week of starting the aripiprazole, the jaw stiffness was accompanied by Parkinsonian symptoms, including bradykinesia, shuffling gait, masked facies, and pill-rolling tremor. Once the aripiprazole was discontinued, the Parkinsonism went away, but the obsessive-compulsive symptoms remained.

DISCUSSION

Case 1: Risperidone (Figure 4). Risperidone, a benzisoxazole derivative, has a high affinity with serotonin 5HT₂, dopamine D₂, α ₁ and α ₂ adrenergic, and H₁ histaminergic receptors and a low to moderate affinity for the serotonin 5HT_{1A}, 5HT_{1C}, and 5HT_{1D} receptors; a weak affinity for the

dopamine D₁ and haloperidol-sensitive sigma site; and no affinity for cholinergic- muscarinic or α ₁ and α ₂ adrenergic receptors.⁶

This case demonstrates one of the more basic concepts of atypical antipsychotics, as risperidone has a potent D₂ receptor antagonism like haloperidol. Several drug trials have shown that 6mg/day of risperidone has greater efficacy than 20mg/day of haloperidol when for improvement of positive and negative symptoms; however, unlike haloperidol, the potential for extra-pyramidal symptoms is much less.⁷ In premarketing studies (Phase II and III), 70 percent of patients were optimally treated with a daily dose of 3mg/day and 90 percent at 6mg/day, with a discontinuation rate due to EPS of only 2.1 percent.⁶ At 6mg/day the risk of EPS was indistinguishable from placebo, but the potential risk for EPS at a dose greater than 6mg daily outweighs the potential therapeutic benefit.^{6,8} Still to be determined is whether the risk of EPS was related to the amount of the dosage increase or due to the rapidity of the increase. Of note, the neuroleptics-naïve individual may have a higher rate of EPS than the chron-

ic schizophrenics that were used in the previous trials.⁹ The old rule of thumb, "Go low and slow," comes to mind.

Case 2: Ziprasidone (Figure 5). Ziprasidone has high affinity for the dopamine D₂ and D₃; the serotonin 5HT_{2A}, 5HT_{2C}, 5HT_{1A}, 5HT_{1D}; α ₁-adrenergic receptors; moderate affinity for the histamine H₁ receptor; and no appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic-muscarinic receptor.¹⁰ The mechanism of action includes being an antagonist at the D₂, 5HT_{2A}, and 5HT_{1D} receptors, and as an agonist at the 5HT_{1A} receptor. Ziprasidone also inhibits synaptic reuptake of serotonin and norepinephrine.

The patient was given an unintentional increased dose of ziprasidone totaling 240mg in a 24-hour period, illustrating the competition between D₂ antagonism and dopamine stimulation being dependent on the dose of the atypical antipsychotic given. In the nigrostriatal tract, the increased dosage resulted in D₂ receptor antagonism prevented dopamine from suppressing acetylcholine, and resulting in a dystonic reaction. The anticholinergic action of diphenhydramine countered the increased acetylcholine in the nigrostriatal pathway, effectively augmenting the mechanism of action of an atypical antipsychotic to parallel a high-potency conventional antipsychotic.

Case 3: Olanzapine (Figure 6). Olanzapine has a high affinity for serotonin 5HT-2A/2C; dopamine D₁-4; muscarinic M₁-5; histamine H₁; and adrenergic α ₁ receptors, and has also been determined to weakly bind to GABAA, benzodiazepine, and α -adrenergic receptors.¹¹ The complaint of akathisia in patient C is consistent with reports from the literature. With an N=248 for olanzapine and N=118 for placebo in a six-week study of adverse events in treatment of schizophrenia with olanzapine, akathisia was noted to be at five percent in the

Case 3: Olanzapine

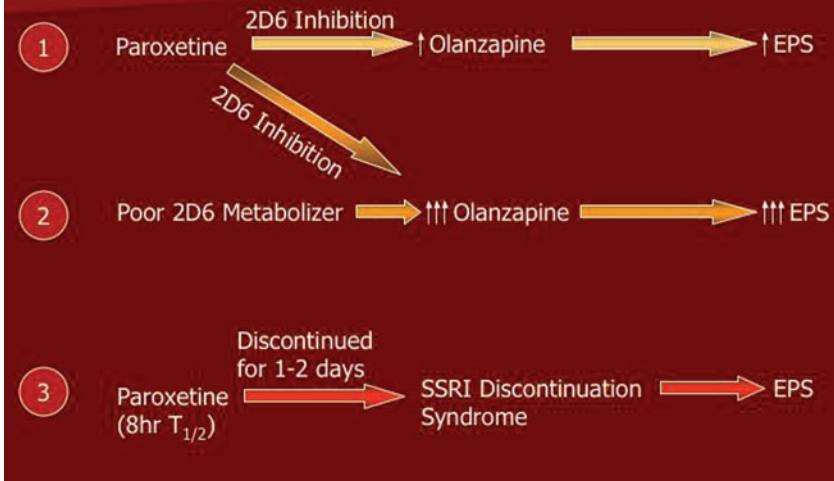


FIGURE 6. 1) Paroxetine causes 2D6 inhibition, leading to increased olanzapine levels that increase the risk of EPS. 2) Poor 2D6 metabolizer coupled with 2D6 inhibition by paroxetine leads to increased olanzapine levels that increase the risk of EPS. 3) Paroxetine's potential for SSRI Discontinuation Syndrome when discontinued has the potential to cause increased risk for EPS.

Case 4: Aripiprazole (Postulated) Mechanism on D₂ Receptors

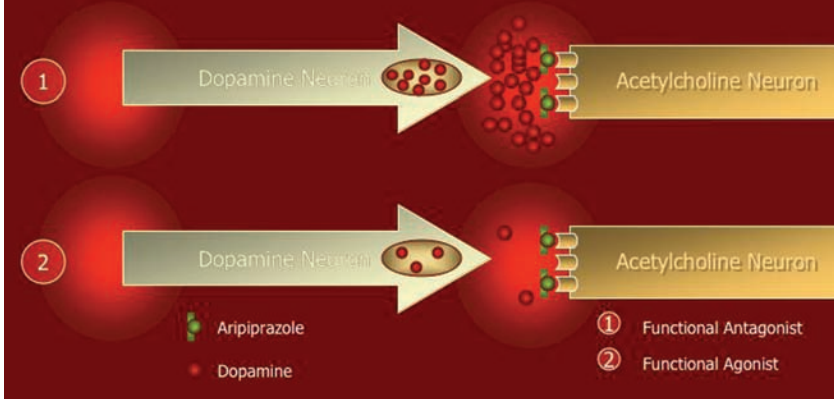


FIGURE 7. 1) Aripiprazole acts as a functional antagonist where dopamine levels are high. 2) Aripiprazole acts as a functional agonist where dopamine levels are low.

test group as compared to one percent for placebo. Assessment for EPS in schizophrenic patients on a fixed dosage of oral olanzapine indicated that akathisia was found to be statistically significant compared to placebo at 10mg±2.5mg per day

(11%–1%) and 15mg±2.5mg per day (10%–1%). Also, any extrapyramidal event was noted to be statistically significant at 15mg±2.5mg per day as compared to placebo (32%–16%). These results appear to be exclusive to oral presentation

and not intramuscularly.

Attention should not only be given to the research showing that akathisia is one of the more common of the EPS symptoms associated with olanzapine, but also the specific psychopharmacological profile of the patient. The patient had been taking paroxetine, a cytochrome P450 2D6 inhibitor. Olanzapine, along with risperidone and clozapine, are atypical antipsychotics metabolized by cytochrome P450 2D6. Given the pharmacologic combination, the patient theoretically could have had increased levels of olanzapine in her bloodstream than would have been expected. Clinical response to an anticholinergic medication raises the suspicion that her symptoms were due to EPS and what role 2D6 inhibition contributed to the increased levels of olanzapine. In addition, the patient may also be a poor 2D6 metabolizer, exposing her to higher levels of olanzapine and subsequent increased risk of akathisia. Another factor to consider is overall medication adherence as paroxetine has the shortest half-life (approximately 8 hours)¹² of the selective serotonin reuptake inhibitors (SSRIs). If she did not take her medications for 1 to 2 days, she may have experienced symptoms of SSRI discontinuation syndrome, another potential etiology of her EPS.¹³

Case 4: Aripiprazole (Figure 7). Aripiprazole has a postulated mechanism of action unlike the other atypical antipsychotics. Although the exact mechanism of action is unknown, the postulated efficacy of aripiprazole is mediated through a combination of partial agonist activity at the D₂ and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors resulting in a slightly different mechanism of action than what is proposed for the other atypical antipsychotics.¹⁴ Aripiprazole has a high affinity for dopamine D₂ and D₃, serotonin 5-HT_{1A} and 5-HT_{2A} receptors; moderate affinity for dopamine D₄, serotonin 5-HT_{2C} and 5-HT₇, α ₁-adren-

ergic and histamine H1 receptors; moderate affinity for the serotonin reuptake site; and no appreciable affinity for cholinergic-muscarinic receptors.¹⁵

While olanzapine is noted to have caused EPS in children and adolescents, no randomized, controlled, clinical trials found EPS in this age group with the use of aripiprazole¹⁶ and only one case report of EPS with aripiprazole in an adolescent 16-year-old female patient.¹⁷ In adults, one clinical trial demonstrated a low incidence of

potential for EPS. In addition to following recommendations for monitoring of weight and blood glucose and serum lipid levels, psychiatrists should also emphasize the need to monitor for EPS and abnormal movements when treating patients with atypical antipsychotics. The effects of atypical antipsychotics on distinct populations such as child/adolescents and the elderly should be studied in detail. Atypical antipsychotics definitely have a place for the treatment of numerous psychiatric disorders, but clini-

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extrapyramidal symptoms at dosages of both 15mg and 30mgs.¹⁸ Further studies should be conducted in both adult and juvenile populations to determine the incidence of aripiprazole induced EPS.

CONCLUSIONS

The cases in this series address the potential to produce extrapyramidal symptoms with four different atypical antipsychotics. As with many classes of medications, unanticipated side effects with the atypical antipsychotics have been identified after years on the market. Even though atypical antipsychotics are considered to produce fewer side effects as compared to conventional antipsychotics, increasing the dosage, whether intentional or by mistake, can lead to higher potential for developing extrapyramidal symptoms. Concomitant usage of other medications also can slow the metabolism of the atypical antipsychotics, thereby increasing the

cians should be aware that this medication class does have the potential to produce troublesome extrapyramidal side effects.

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